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CITATION:

Kobayashi, Yusuke ...[et al]. Direct N-Glycofunctionalization of Amides with Glycosyl Trichloroacetimidate by Thiourea/Halogen Bond Donor Co-Catalysis. Angewandte Chemie 2018, 57(14): 3646-3650

ISSUE DATE:

2018-03-26

URL:

http://hdl.handle.net/2433/243151

Direct *N*-glycofunctionalization of amides with glycosyl trichloroacetimidate by thiourea/halogen bond donor co-catalysis

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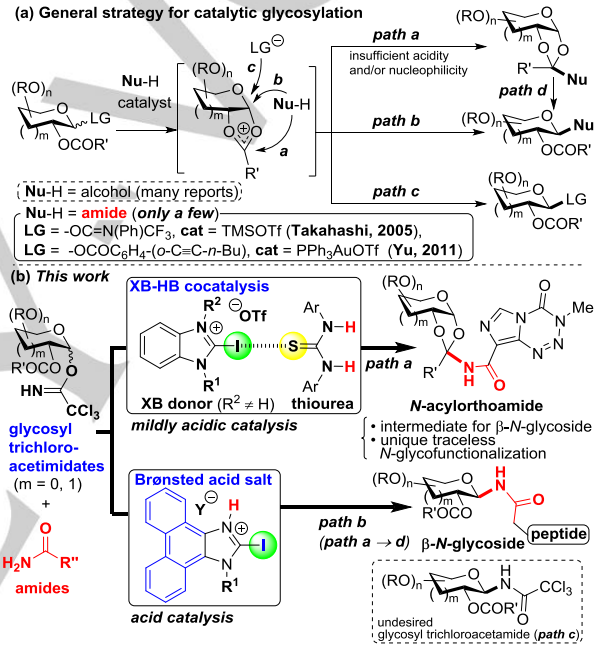
Abstract: *Using a halogen bond (XB) donor and Schreiner's thiourea as cooperative catalysts, various amides, including the asparagine residues of several peptides, were directly coupled with glycosyl trichloroacetimidates to give unique N-acylorthoamides in good yields. Synthetic applications of N-acylorthoamides, including rearrangement to the corresponding β-N-glycoside, were also demonstrated.*

N-Glycosides are found in various pharmaceuticals, biologically active compounds, and natural products.[1] They can be used in material science as glycolipids for lipid nanotubes.[2] Sugar moieties are known to impart hydrophilicity to molecules, and alter the higher order structure and bioavailability of molecules.[3] Several *N*-glycosides have been utilized as prodrugs to improve delivery to target tissues and organs.[4] However, synthetic methodologies for *N*-glycosylamides are not as well developed[5–8] as those for *O*-glycosides (Scheme 1a).[9] Among the reported synthetic methods for *N*-glycosylamides,[6] direct *N*-glycosylation of amides is the most straightforward but challenging approach because of the poor nucleophilicity of the amides, and only limited catalytic conditions have been reported to date.[8] However, there still remains to be improved concerning scope of amides and the accessibility of Leaving group (LG). In fact, direct introduction of asparagine residues of peptides have been rarely investigated, and the use of tripeptide significantly decreased the chemical yield,[8a] as compared with that of dipeptide.[8a,c] We then focused on the utilization of glycosyl trichloroacetimidates,[10] which are regarded as one of the most readily available glycosyl donors and activated under relatively mild condition.[11a,b] On the other hand, undesired glycosyl trichloroacetamide was obtained as byproduct, especially when the glycosyl acceptor (Nu-H) has low nucleophilicity (path c).[8a] Herein, we report two different catalytic systems, which offers a solution to these problems (Scheme 1b). We envisaged that the activation of glycosyl trichloroacetimidates under mildly acidic condition would afford kinetically favored product by the preferential addition of employed amides via *path a*.[10] We thus focused on Schreiner's thiourea,[12] whose pK_a value was reported to be 8.5 in DMSO.[12c] Although thiourea have been recently employed for glycosylation[11] and acetalization[13] of alcohols, its acidity was insufficient to activate trichloroacetimidate.[11a,b] We envisioned that a soft and mild Lewis acid, such as 2-iodoazolium salt[14] ($R^2 \neq H$) as halogen bond (XB) donor,[15–17] used as a co-catalyst would interact with the soft Lewis basic moiety of thiourea[18] to increase the HB-donating ability of thiourea,[19] so that the LG could be activated[20] with wide functional group tolerance. The produced *N*-acylorthoamides[21] would serve as intermediates for thermodynamically favored β-*N*-glycosides[10] (Scheme 1a, path d, Nu = amide), and offer a unique traceless *N*-glycofunctionalization of amide, impacting on prodrug synthesis. In fact, during the course of our investigation on the rearrangement of *N*-acylorthoamide to *N*-glycoside (*path d*), we have developed a new type of Brønsted-acid-salt catalyst, comprised of Brønsted acid and 2-halogenated azole, which was found to be an efficient catalyst for the direct *N*-glycosylation of various amides utilizing the same glycosyl trichloroacetimidates (*path b* and/or *path a* and *d*).



Scheme 1. Summary of this work

We first screened various catalysts for the direct *N*-glycofunctionalization of a protected asparagine derivative **2a**[8] with a readily accessible glycosyl donor **1**[22a] (Table 1). The use of Schreiner's thiourea (**5**) on its own did not promote the reaction at all (entry 1). We next investigated several co-catalysts for activation of thiourea,[19] including metallic Lewis acids (entries 2–5)[11c] and Brønsted acids (entries 6–7).[11a] Interestingly, when a substituted diarylphosphoric acid was employed, an *N*-acylorthoamide **4a**, whose structure was fully characterized using spectral data (Figure S5), was obtained in 22% yield (entry 6). A stronger Brønsted acid resulted in the production of **3a**, albeit in 26% yield (entry 7), indicating that the acidity of the catalyst affects production of **3a**. Indeed, as previously reported, with 10 mol % of trimethylsilyl trifluoromethanesulfonate (TMSOTf)[8] as a conventional Lewis acid, the donor **1** was immediately consumed, and **3a** was obtained in 25% yield (entry 8), along with several inseparable byproducts. As the results were not satisfactory, we next investigated several XB donors as cooperative catalysts (entries 9–12). We found that combination of thiourea **5** with 2-iodobenzimidazolium-type XB donors **7b**[14] afforded **4a** as a major product in 66% yield (entry 11). A newly designed XB donor with extended aromatic rings **7c** similarly afforded **4a** as the major product (entry 12). The XB donor **7b** on its own did not afford the target products (entry 13), which indicated that combination of thiourea **5** and XB donor **7b** was

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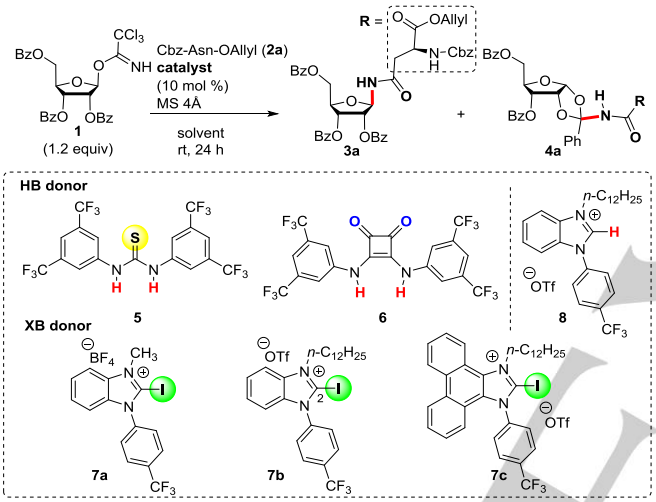
essential for production of **4a**. The yields of **4a** greatly decreased when the squaramide[23] **6**, which has superior HB-donating ability[23c] to thiourea,[12b,c] was employed instead of **5** (entries 14 and 15). In addition, a control experiment using non-halogenated azolium salt **8** did not afford **4a** at all (entry 16). These results suggest that the reaction was not accelerated by the azoliium cation moiety or triflate anion by itself,[24] and that XB formation between the sulfur atom of **5** and the iodine atom of XB donor **7**[15d,18a,b,d] plays an important role for the promotion of the reaction, presumably through the activation of LG (Scheme S1).[25] Although other solvents, such as THF, toluene, and acetonitrile, can be used for this reaction without significant decrease of the chemical yields (entries 17–19), CH_2Cl_2 was chosen for further investigation in terms of the solubility of various amides. To gain further support for the XB formation, a ^{13}C NMR experiment was performed using thiourea (**5**) and XB donor (**7b**) (Figure S2).[25] When 1.0 equivalent of **5** was added, the ^{13}C NMR peak of the C2 position of **7b** broadened and shifted downfield in accordance with previous reports on XB interaction of the iodoazolium salts.[14f-i]

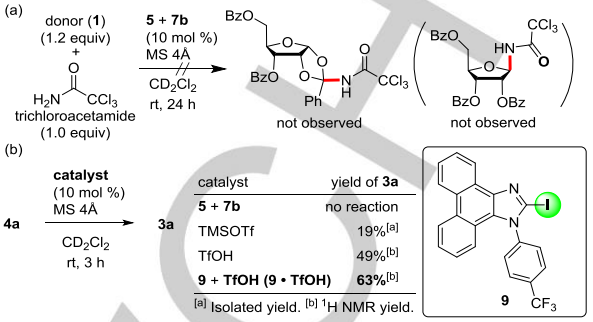
Table 1: Screening of reaction conditions for orthoamide **4**



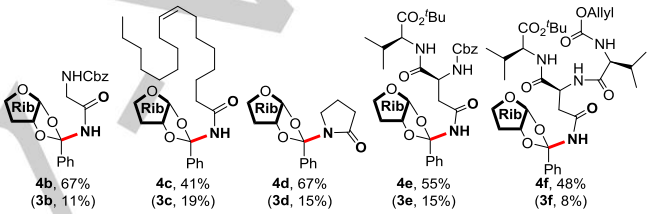
entry	catalyst	solvent	**3a** (%)[a]	**4a** (%)[a]
1	**5**	CH_2Cl_2	0[b]	0[b]
2	**5** + BF_3•OEt_2	CH_2Cl_2	7	0[b]
3	**5** + $Sc(OTf)_3$	CH_2Cl_2	0[b]	0[b]
4	**5** + $AuCl_3$	CH_2Cl_2	trace	0[b]
5	**5** + PPh_3AuOTf	CH_2Cl_2	trace	0[b]
6	**5** + $(4\text{-}NO_2C_6H_4O)_2P(O)OH$	CH_2Cl_2	0[b]	22
7	**5** + TfOH	CH_2Cl_2	26	0[b]
8[c]	TMSOTf	CH_2Cl_2	25	0[b]
9	**5** + C_6F_5I	CH_2Cl_2	0[b]	0[b]
10	**5** + **7a**	CH_2Cl_2	5	32
11	**5** + **7b**	CH_2Cl_2	7	**66**
12	**5** + **7c**	CH_2Cl_2	8	**63**
13	**7b**	CH_2Cl_2	0[b]	0[b]
14	**6** + **7b**	CH_2Cl_2	2	19
15	**6**	CH_2Cl_2	0[b]	0[b]
16	**5** + **8**	CH_2Cl_2	0[b]	0[b]
17	**5** + **7b**	THF	3	64
18	**5** + **7b**	toluene	15	66
19	**5** + **7b**	CH_3CN	4	53

[a] Isolated yields. [b] Not detected. [c] 58% of **2a** was recovered.

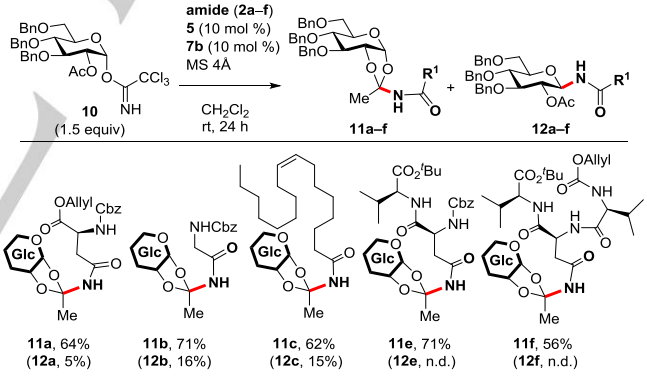
It is worth noting that under the optimized condition (Table 1, entry 11), neither *N*-trichloroacetylorthoamide nor glycosyl trichloroacetamide were obtained, even additional trichloroacetamide (1.0 equiv) was employed (Scheme 2a), presumably due to the inherent reactivity of the acyloxonium ion intermediate toward nucleophiles.[10] Encouraged by this result, we then investigated the efficient catalysts to promote the rearrangement of **4a** to **3a** (Scheme 2b). Although the chemical yields of **3a** were low using TMSOTf[10c] and TfOH as catalysts, partly because of the degradation of **4a**, Brønsted acid salt **9•TfOH,** synthesized from the same intermediate for **7c,** was found to be most suitable.



Scheme 2: (a) Control experiment using trichloroacetamide (b) Catalytic rearrangement of **4a** to **3a**



Scheme 3: Substrate scope for the synthesis of *N*-acylorthoamides **4**. Isolated yields were indicated. Rib = ribose.

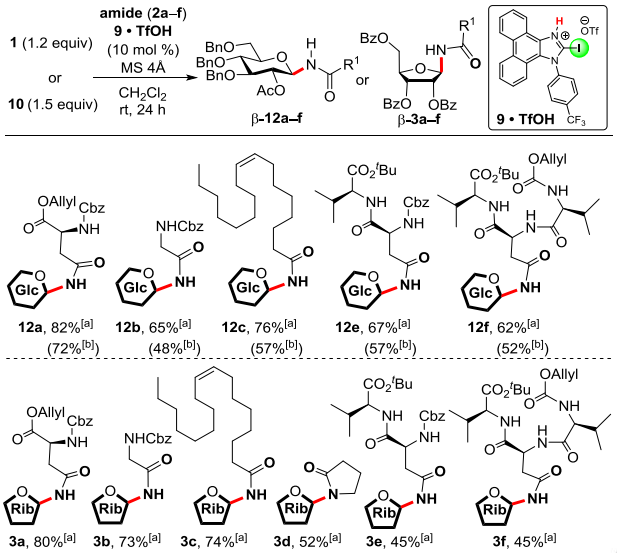


Scheme 4: Substrate scope for the synthesis of *N*-acylorthoamides **9**. Isolated yields were indicated. Glc = glucose. N.d. = not detected.

Having established the synthetic utilities of *N*-acrylorthoamide **4**, we next investigated the substrate scope for glycosyl donors and amides (Scheme 3, 4). Using 10 mol % of catalysts **5** and **7b**, *N*-Cbz-glycineamide (**2b**) could be directly converted into **4b** in 67% yield. Oleamide (**2c**), which is an important amide towards the synthesis of lipid nanotubes,[2] was effectively conjugated with sugar to afford **4c** in 41% yield. Notably, the asparagine residues of dipeptide and tripeptide were glycosylated by the present co-catalytic system to afford **4e** and **4f** in unprecedented good yields (Scheme 3). The same amides were also coupled with the glucose surrogate utilizing 3,4,6-tri-*O*-benzyl-2-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate (**10**)[22b] to yield *N*-acylorthoamides **11a–f** in 56–71% yields (Scheme 4).

We next focused on the direct *N*-glycosylation utilizing Brønsted acid salt **9•TfOH** (Scheme 5), as the acidity of the catalyst was supposed to be important to obtain *N*-glycoside **3a** in Table 1 (entry 7, 8). To our delight, *N*-glycoside **12** was obtained in 72% yield, when glycosyl donor **10** and amide **2a** were reacted. A slight improvement of the

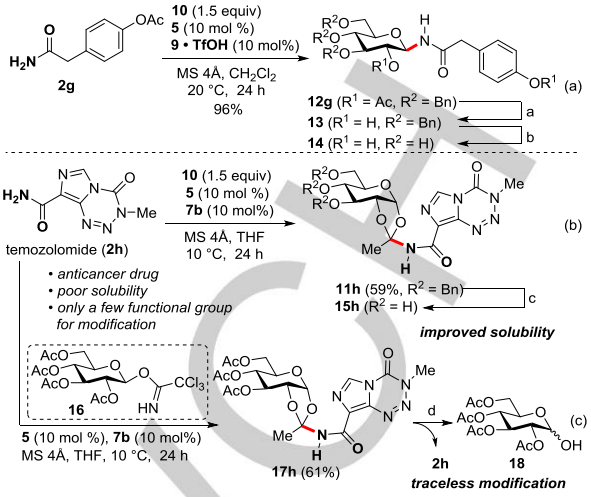
yield was observed when thiourea **5** was employed as co-catalyst.[26] Under the optimized reaction conditions, a series of *N*-glycoside **12a–f** were obtained in 62–82% yields as single β-isomers. In addition to the glucose-derived donor **10**, a ribose-derived donor **1** could be directly incorporated into amides to afford the corresponding adducts in 45–80% yields. Again, the conjugation with tripeptide proceeded with unprecedented good yields. Notably, the catalyst **9•TfOH** could be readily prepared from the commercial source in three steps with high yields, and found to be air- and moisture-stable for several months.



Scheme 5: Substrate scope for direct *N*-glycosylation using catalyst **9•TfOH**. [a] With 10 mol % of **5**. [b] Without **5**. Glc = glucose, Rib = ribose.

The utilities of the present reactions have been clearly demonstrated by their application to the syntheses of natural products[27] (Scheme 6a), and the modification of pharmaceuticals to prodrugs (Scheme 6b). The direct *N*-glycosylation of a substituted 2-phenylacetamide **2g** with glycosyl donor **10** proceeded very smoothly to obtain the desired adduct **12g** in excellent yield. The successive deprotection of acetyl and benzyl groups afforded the product in almost quantitative yield (Scheme 6a). The methodologies developed in this paper are particularly useful when the compound to be functionalized has only an amide group for a traceless modification, and this strategy is especially true for pharmaceuticals. For example, the anticancer drug temozolomide (**2h**) can be transformed into the corresponding *N*-acylorthoamide **11h** using glycosyl donor **10** with 10 mol % of **5** and **7b** in THF. After deprotection of the benzyl group of **11h**, the product **15h** was found to be soluble in protic solvents, such as methanol, while temozolomide itself is almost insoluble.[28] Practically, commercially available glycosyl donor **16** can be converted into the corresponding adduct **17h** in 61% yield. It was noted that hydrolysis of the *N*-adduct **17h** under mildly acidic conditions afforded temozolomide (Scheme 6c).

In conclusion, we have developed two different catalytic systems for the synthesis of *N*-acylorthoamides and *N*-glycosides with wide functional group tolerance. The XB interaction plays an important role in the production of *N*-arylorthoamides via the activation of LG under mildly acidic condition. The combination of a XB donor with a relatively soft XB acceptor will allow for otherwise inaccessible transformations, and broaden the utility of XB donor catalysis. In addition, halogenated azolium salts **9•TfOH** can be utilized for direct *N*-glycosylation as novel bench-stable Brønsted acid. Both methodologies will be powerful for the molecular transformation of amides, and offer a new tool for the traceless modification of pharmaceuticals. Further investigation on the details of the reaction mechanism, including complexation of amides, and substrate scope is now underway in our laboratory.



Reagents and conditions: [a] NaOMe, MeOH, rt, 12 h, 88%. [b] Pd/C (10 mol %), H_2 (1 atm), MeOH, rt 2 h, quant. [c] Pd/C (10 mol %), H_2 (1 atm), EtOAc, rt, 2 h, 60%. [d] *p*-TsOH, DME/H_2O, rt, 24 h, 79%

Scheme 6: Application of the present *N*-glycofunctionalization

Experimental Section

To a stirred solution of glycosyl donor **1** (36.4 mg, 0.06 mmol) and amide **2a** (1.0 equiv, 0.05 mmol) in DCM (1.0 mL) was added activated MS 4Å (50 mg), and the reaction mixture was stirred at the ambient temperature for 10 min. Then, the catalysts **5** (2.5 mg, 10 mol %) and **7b** (3.5 mg, 10 mol %) were added, and the resulting mixture was stirred at the ambient temperature for 24 hours. After the MS 4Å was filtered off and washed with chloroform, the filtrate was concentrated under reduced pressure to give crude *N*-acylorthoamide, which was purified by silica gel column chromatography to afford **4a** (24.8 mg, 66%), along with **3a** (2.6 mg, 7%).

Acknowledgements

This work was partly supported by JSPS KAKENHI (Grant Number 16H06384 and 17K15423). We also acknowledge funding from the Society of Iodine Science (SIS). We thank Dr. Hiroyasu Sato (Rigaku Corporation) for the assistance of X-ray analysis.

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[25] See the Supporting Information for details.

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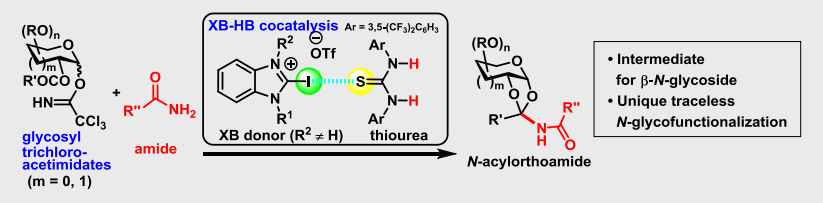

Using a halogen bond (XB) donor and Schreiner's thiourea as cooperative catalysts, various amides, including the asparagine residues of several peptides, were directly coupled with glycosyl trichloroacetimidates to give unique N-acylorthoamides in good yields. Synthetic applications of N-acylorthoamides, including rearrangement to the corresponding β-N-glycoside, were also demonstrated.

Keywords: glycosylation • organocatalyst • XB donor

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Direct *N*-glycofunctionalization of amides with glycosyl trichloroacetimidate by thiourea/halogen bond donor co-catalysis